

A newly discovered etiology for infectious pulmonary nodules: “The rickettsial infection”

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ABSTRACT

Rickettsial infection as the cause for multiple pulmonary nodules is not previously been reported. We report two cases of rickettsial infection with multiple bilateral pulmonary nodules which is the first of its kind in the world literature. Both cases improved with doxycycline and follow-up lung imaging showed the disappearance of all pulmonary nodules after 6 weeks.

Key words: Gram negative, Pulmonary nodules, Rickettsial infection

Rickettsiae are intracellular Gram-negative organisms that parasitize the intestinal canal of arthropods [1]. They do not stain well with Gram stain and they have Gram-negative cell walls that lack flagella. Their genome is small composed of 1–1.5 million bases [2,3]. These organisms, once they gain access to humans, multiply in capillary endothelial cells, producing lesions in the skin, central nervous system, heart, lungs, liver, kidneys, and skeletal muscles [1]. Rickettsial infections are one of the most common tick-borne infections, especially in developing countries like India. Eleven outbreaks have been reported from 2000 to 2011, with more than 900 cases and 42 deaths (case fatality rate of 5–17%) [4].

A serosurvey done by the National Centre for Disease Control in Delhi among patients with fever of unknown origin showed 8.2% positivity for rickettsial disease using the Weil-Felix test in a series of 737 cases [5]. When the test was assessed in clinically suspected rickettsial disease, it was positive in 33.3% of which scrub typhus around 48.2%, spotted fever in 27.5%, and typhus group in 6.8% [5]. From 2000 to 2018, there were around 2090 cases reported from India [6]. The disease can affect multiple systems and a high index of suspicion is crucial in diagnosing the case. It can present with multiorgan dysfunction and is having high mortality [7]. High associated morbidity and mortality have made pathogenic rickettsiae a bioterrorism agent [8].

Here, we report two cases of rickettsial infection with multiple bilateral pulmonary nodules which is the first of its kind in the world literature. This case series has a significant impact

on treating physicians in evaluating pulmonary nodules and illustrates that not all nodules are malignant. This case series also helps in avoiding unnecessary invasive procedures that may be detrimental to the patients. Both cases improved with doxycycline and follow-up lung imaging showed the disappearance of all pulmonary nodules after 6 weeks.


CASE REPORT

Case 1

A 52-year-old female presented with complaints of high-grade fever, cough, and breathlessness for 5 days. She was tachypneic (respiratory rate – 32/min), febrile (103°F), and restless at the time of admission. On clinical examination, she had icterus and systemic examination was normal except for decreased air entry in the left infrascapular, axillary, and infra-axillary regions. Her routine blood investigations showed elevated total count (24,700/mm³) with neutrophil predominance (neutrophils – 82.7% and lymphocytes – 10.6%). She also had thrombocytopenia (59,000/mm³). Her reports showed elevated C-reactive protein (CRP) (36.2 mg/dl, reference – 0.0–1.0) with an erythrocyte sedimentation rate (ESR) of 45 mm/h. Her liver function test was also deranged (total bilirubin – 5.20 mg/dl, direct – 2.5 mg/dl, SGOT – 180.6 U/L, SGPT – 369.5 U/L, and alkaline phosphatase – 241 U/L). Renal function tests and serum electrolytes were normal. An infectious work-up including blood, urine, and sputum cultures which were sterile. Other common infectious work-up including leptospirosis, human immunodeficiency virus, hepatitis

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B surface antigen, and hepatitis C virus which were inconclusive. A connective tissue disease work-up including anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies, and rheumatoid arthritis factor which were all negative.

Considering the prevalence of rickettsial infection in the locality, a Weil-Felix test was done which showed significantly high titers (OX 2 – 1:1280, reference – <1:40). A rickettsial polymerase chain reaction (PCR) was done to further confirm the diagnosis. As the patient had predominant respiratory symptoms and chest X-ray showing left lower zone opacity, a computerized tomographic (CT) thorax was also done, which showed bilateral multiple pulmonary nodules with the left lower lobe posterior basal segment solid soft-tissue density subpleural lesion (2×1.9 cm) and multiple other subpleural nodules of size <10 mm (Fig. 1). She responded to oral doxycycline at a dose of 100 mg twice daily for 10 days. She was followed up with a repeat CT thorax after 6 weeks and was normal (Fig. 2).

Case 2

A 32-year-old young female presented with a history of high-grade fever and lower respiratory symptoms. She also had icterus and congested conjunctiva. She had tachypnea (respiratory rate – 28/min), febrile (102°F), and was toxic. Her routine blood investigations showed elevated total count (18,500/mm³) with neutrophil predominance. She had elevated CRP (23.2 mg/dl, reference – 0.0–1.0) with an ESR of 60 mm/hr. Like the previous case, this patient was also having features of acute infectious hepatitis (total bilirubin – 7.5 mg/dl, direct – 6.7 mg/dl, SGOT – 44 U/L, SGPT – 134 U/L, and alkaline phosphatase – 218 U/L). A Weil-Felix test done showed high titers (OX 2 – 1:320, ref – <1:40). This patient had a 12 X 10 mm subpleural nodule in the right upper lobe posterior segment similar to the previous case as shown in CT (Fig. 3).

She was managed with oral doxycycline at a dose of 100 mg twice daily for 10 days. She responded to treatment, her chest signs improved, hepatitis resolved, and became afebrile. As we lost follow-up, we were not able to reassess the nodule in this case.

DISCUSSION

Tropical infections like the rickettsial infections are reemerging. The predominant classification includes the spotted fever group and the typhus group. These microorganisms exert their pathologic effects by adhering to and invading the endothelial lining of the vasculature of various organs affected. It is associated with increased vascular permeability and edema, loss of blood volume, hypoalbuminemia, decreased osmotic pressure, and hypotension. It is also associated with thrombosis and vasculitis with even septic emboli. In our case series, both the patients were toxic at presentation and had hepatopulmonary manifestations with elevated acute inflammatory markers.

Males have a higher risk for infection with tick-borne rickettsioses [9]. This may be due to more recreational or

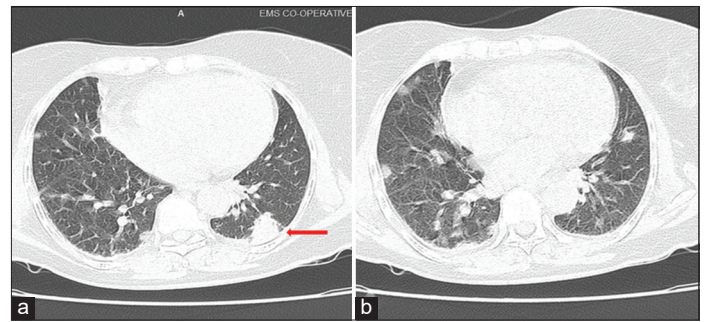


Figure 1: Computerized tomographic thorax at the time of admission. (a) Arrow showing a larger subpleural nodule in the left lower lobe 2×1.9 cm; (b) multiple nodules (Case 1)

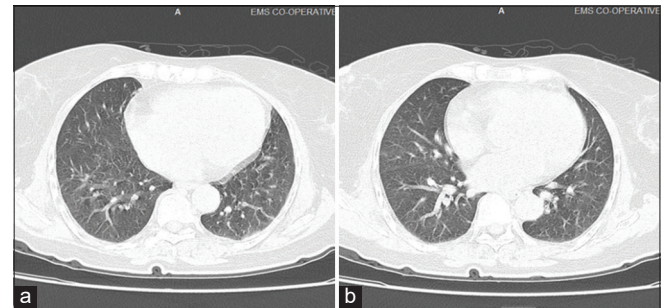


Figure 2: (a) Computerized tomographic (CT) thorax at follow-up after 6 weeks; (b) repeat CT showing clearance of nodules (Case 1)

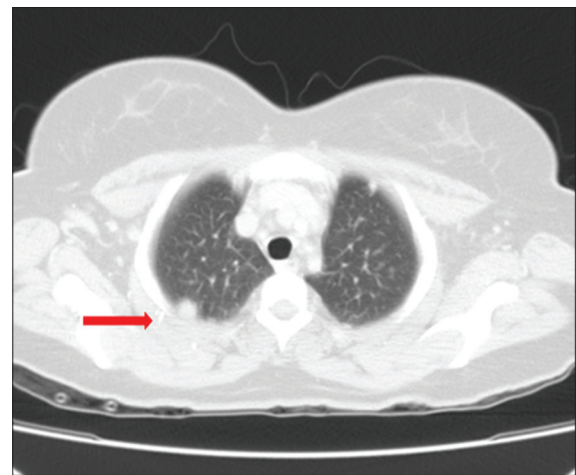


Figure 3: Computerized tomographic image showing subpleural nodule. Arrow showing subpleural nodule in the right upper lobe (Case 2)

occupational exposures to tick habitats. In our case series, both were females, but they were involved in occupational activities prone to rickettsial infections.

Early signs and symptoms of these infections are mostly non-specific and may mimic benign viral illnesses which make diagnosis difficult. They may present with fever, headache, rash, confusion, myalgia, cough, and other systemic symptoms depending on the organ involvement.

Both the cases had features of the hepatopulmonary syndrome. The liver function tests were deranged in both cases with elevated liver enzymes. They had thrombocytopenia with elevated ESR. Renal function was normal in both cases. Pulmonary

manifestations may range from atelectasis to infiltrates or pulmonary edema [10]. Our cases had a different pulmonary manifestation in the form of multiple pulmonary nodules which is not previously reported in the literature. A pulmonary nodule is a small round or oval-shaped growth in the lung. It can be benign or malignant. Infections are the most common cause for benign pulmonary nodules and *Mycobacterium tuberculosis*, fungal infections such as aspergillosis, histoplasmosis, and coccidioidomycosis being the more prevalent.

Rickettsial infection as the cause for multiple pulmonary nodules is not previously reported in world literature [11]. Our cases had pulmonary nodules which were documented by CT imaging and resolved completely after treatment. This suggests the importance of suspecting rickettsial infection as the cause for infectious lung nodules. This also helps to avoid unnecessary invasive procedures like a guided biopsy. The differential diagnosis for rickettsial infection includes leptospirosis, dengue fever, malaria, viral hemorrhagic fever, and even certain vasculitis.

The history of travel, occupation, and tick bite is very important as the specific diagnosis is often challenging. These tropical infections are often difficult to diagnose clinically but in some cases, the classical eschar is pathognomonic. It is possible to rule out other infections that may mimic rickettsia by doing tests such as peripheral smear for malaria at fever spike, IgM Leptospira enzyme-linked immunosorbent assay (ELISA) and blood cultures for leptospirosis, dengue NS1, and IgM ELISA for dengue fever. No rapid laboratory tests are available to diagnose rickettsial diseases early in the course of illness. We have confirmed the case with the Weil-Felix test and rickettsial PCR tests. Serological tests are always the mainstay of diagnosis.

The differential diagnosis for lung nodules includes infectious causes such as tuberculosis, histoplasmosis, and certain viral and fungal infections. The non-infectious causes include benign and malignant tumors. A proper clinical history is important in evaluating lung nodules as malignant lesions including secondary's are a concern. Invasive procedures like guided biopsies may be avoided in infectious cases which improve on treatment.

The overall mortality rate is 4%, despite effective antibiotic therapy. This may be due to the delay in the diagnosis and initiation of proper treatment. Those treated during the 1st week of illness have the highest chance of complete recovery; however, if the disease is allowed to progress to the 2nd week untreated, even optimal therapy progressively becomes less effective [12]. Fever usually subsides within 24–72 h after starting antibiotic therapy.

In both cases, they responded well to doxycycline and became afebrile with improvement in liver function and lung signs in due course. Treatment may be terminated 2–3 days after the patient is afebrile and at least 10 days of therapy has been given [13].

CONCLUSION

The rickettsial infection should be considered as one common cause for infectious pulmonary nodule which responds well to doxycycline. Invasive procedures and investigations may be deferred in such a scenario.

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